UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,573	02/07/2006	Anita Mehta	RLL-256US	5274

26815 7590 07/09/2007

RANBAXY INC.
600 COLLEGE ROAD EAST
SUITE 2100
PRINCETON, NJ 08540

EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	

MAIL DATE	DELIVERY MODE
07/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

dosage form requirements when selecting a salt form for development. Since the choice of counter-ion affects the properties of salt forms [3,4], salt selection studies involve the preparation of a number of different salts using a variety of pharmaceutically acceptable acids or bases with differing properties (e.g., acidity/basicity, molecular size, shape, flexibility, etc.). The relevant physicochemical properties of each salt are characterized, including degree of crystallinity, hygroscopicity, aqueous solubility, crystal habit, and physical and chemical stability. Based on these properties of the salt forms, their suitability for development can be evaluated. Several strategies for streamlining and optimizing salt selection procedures have been reported, including in-situ techniques for ranking the solubility of salts [63], tiered approaches in which the least time-consuming studies are carried out first and used to remove from consideration salts that are not viable [64]. One issue not readily considered by existing strategies is the polymorphism and solvate forming behavior of the different salt forms of a compound, which could be used as an additional criterion when more than one salt may be viable, but the degree of polymorphism and solvate formation of each may become a criterion for form selection.

HT crystallization technologies have been used to more rapidly and comprehensively identify the range of salt forms that may be prepared for a given compound or series of compounds, and characterize their crystal form diversity (polymorphs, solvates, hydrates). However, only a few studies have been published or presented. Several HT salt selection studies on well-characterized pharmaceutical compounds have been carried out to demonstrate the power of these technologies in solid form discovery. For example, in a small HT study (i.e., 96 wells) on the antibacterial sulfathiazole, salt formation was explored using varying stoichiometric ratios of pharmaceutically acceptable organic and mineral bases in an array of solvent conditions [65]. The screen resulted in the rapid identification and characterization of 10 salt forms and showed that the salts exhibited a range of melting points depending on the counter-ion type and stoichiometric ratio. Similar HT salt selection experiments on caffeine and naproxen resulted in the identification of numerous salts of each compound [47,50,51].

In the discovery phase, HT crystallization has been used to identify soluble salt forms of compounds during ELO to facilitate early animal dosing, thereby providing the ability to uncover underlying chemical and/or biological responses elicited by candidate molecules, including toxicity or efflux [46,59]. Such information permits rapid identification of problematic compounds or scaffolds, allowing resources to be directed to projects with greater opportunity for success. HT crystallization can facilitate selection of leads that are more likely to survive preclinical development. HT crystallization has been used successfully to identify multiple new salt forms and the polymorphs and solvates of each compound belonging to two discovery programs using less than 200 mg of compound per screen [59]. Approximately 150–200 experiments were performed on each compound using a library of pharmaceutically acceptable acids or bases with an array of solvent compositions and process conditions. Each screen resulted in discovery of multiple new salt forms, and in some cases polymorphs and solvates. Interestingly, similar salt types were identified for each compound in a given series, as illustrated in Fig. 5, where the frequency of occurrence is plotted as a function of counter-ion for each discovery series. Clear trends in the degree of solid form diversity of salt forms, including polymorphism and solvation behavior, were also evident within each compound series. These data indicate the potential for identifying salts suitable for most compounds tested in a particular scaffold or series, based on analysis of only a portion of the series, i.e., a platform-based approach to salt selection, provided the chemistry surrounding the ionizable functionality is not significantly altered during further structure–activity relationship (SAR) development. Furthermore, solubility measurements of each salt form in physiologically relevant fluids allowed ranking of salt forms in a given series, and comparison of salts between series was also possible. The average turnaround time per screen was approximately 2 weeks, such that feedback on the physicochemical properties of each compound was provided to the medicinal chemists on a similar time scale as potency, selectivity and metabolism screens.

Salt selection is normally part of the standard preformulation studies carried out during preclinical development, where rapid identification of the possible salts of a compound and their properties can facilitate product development. To further facilitate

Office Action Summary	Application No.	Applicant(s)	
	10/520,573	MEHTA ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/07/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-29 are pending in the instant application, of which **Claim 6** is currently amended.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on 02/07/2007 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8-12 & 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of the formulae I-V; including enantiomers, diastereomers, N-oxides and pharmaceutically acceptable salts thereof; the specification is not enabled for *solvates, esters, polymorphs, prodrugs or metabolites* thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Nature of the Invention

The nature of the invention in **Claims 1-5, 8-12 & 20** are the compounds of formulae I-V, and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The state of the prior art and the predictability or lack thereof in the art

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development

candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization, (Morissette *et al.* Advanced Drug Delivery Reviews **2004**, *56*, 275-300).

For instance, the phenomenon of polymorphism, in the crystallization of organic compounds, is of crucial importance to the pharmaceutical industry. Two polymorphs of the same drug molecule may have different physical properties: e.g. solubility, bioavailability, melting points, density, hardness, or color; and may have dramatically different properties that effect the scale-up process. Due to the differences between polymorphs, the drug regulatory authorities (e.g. the FDA) are increasingly demanding more information about potential drug products before granting approval. The conditions under which polymorphs interconvert is also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling, compression, and storage. Therefore, for these reasons, the state of the prior art is one of unpredictability. The science of crystallization has evolved such that said differences in properties implies patentable distinctiveness between polymorphs.

Amount of direction/guidance & presence or absence of working examples

There is guidance for the preparation of the compounds in the specification; however, no direction or guidance is present in the instant specification for the preparation of solvates, esters, polymorphs, prodrugs, and metabolites for the compounds of formulae I-V. Also, there are no working examples present in the disclosure for solvates, esters, polymorphs, prodrugs, and metabolites for the compounds of formulae I-V. Therefore, one of skill in the art would be required to identify the correct solvent system and crystallization technique for each compound and, further, identify the similarities and differences between crystals and corresponding spectral data for each compound (polymorph) in order to determine what is being claimed.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include compounds of formulae I-V, and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The quantity of experimentation necessary

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any solvates, esters, polymorphs, prodrugs or metabolites of a compound according to formulae I-V as instantly claimed. The science of crystallization has evolved such that, without

guidance or working examples for polymorphs in the specification, the claims lack enablement. This rejection can be overcome by deletion of the words: solvates, esters, polymorphs, prodrugs, and metabolites from **Claims 1-5, 8-12 & 20.**

Claims 8-12 & 18 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compositions and a method of *treatment* for some diseases or disorders of the respiratory, urinary and gastrointestinal systems, (such as those listed in **Claims 13-17 & 19**: urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis), it does not reasonably provide enablement *for the treatment or for the prophylaxis* for any diseases or disorders of the respiratory, urinary and gastrointestinal systems. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention is compounds and compositions of formulae I-IV, the process for preparing these compounds, and methods of using these compounds.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities,

which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. *In the instant case*, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for conditions such as urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis, but it does not mean that the same group of compounds and compositions may prevent said conditions.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for the *prophylaxis* of diseases or disorders of the respiratory, urinary and gastrointestinal systems as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of formulae I-IV to

treat clinical conditions such as urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis is found on pages 14-16.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 8-12 & 18 are drawn to "the treatment or prophylaxis ..." Prophylaxis is commonly known to be synonymous with prevention. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Deleting the word "prophylaxis" in **Claims 8-12 & 18** and incorporating the limitations of **Claims 13-17 & 19** into **Claims 8-12 & 18,** respectively, can overcome this rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over **Claims 1-38** of U.S. Patent No. **7,232,835** (US Serial No. **10/537,851**). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to overlapping subject matter, (specifically when **Q** = $(CH_2)_n$, **n** = 0 and **Z** = NR_{10}). The compounds of the current application are not patentably distinct from those of the **'835** Patent because of the significant overlap within formulae I-V of each case. Therefore, potential infringements upon the instant application would also be infringements upon the **'835** Patent.

Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over **Claims 1-32** of US Serial No. **10/543,585**. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to overlapping subject matter, (specifically when **Q** = $(CH_2)_n$, **n** = 0 and **Z** = NR_{10}). The compounds of the current application are not patentably distinct from those of the **'585** application because of the significant overlap within formula I of each case. Therefore, potential infringements upon the instant application would also be infringements upon the **'585** application.

Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over **Claims 1-28** of US Serial No. **10/552,455**. Although the conflicting claims are not identical, they are not

patentably distinct from each other because they are drawn to overlapping subject matter, (specifically when **Q** = $(CH_2)_n$, **n** = 0 and **Z** = NR_{10}). The compounds of the current application are not patentably distinct from those of the **'455** application because of the significant overlap within formula I of each case. Therefore, potential infringements upon the instant application would also be infringements upon the **'455** application.

Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over **Claims 1-14** of US Serial No. **10/552,456**. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to overlapping subject matter, (specifically when **Q** = $(CH_2)_n$, **n** = 0 and **Z** = NR_{10}). The compounds of the current application are not patentably distinct from those of the **'456** application because of the significant overlap within formula I of each case. Therefore, potential infringements upon the instant application would also be infringements upon the **'456** application.

Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over **Claims 1-17** of US Serial No. **10/544,520**. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to overlapping subject matter. The compounds of the current application are not patentably distinct from those of the **'520** application because of the significant overlap within formula I of each case,

(specifically, when **Q** = bond). Therefore, potential infringements upon the instant application would also be infringements upon the **'520** application. *Note*: the structure of Formula I in the **'520** application appears to be incorrect, (it is missing a bond, making it monocyclic). However, it appears to Examiner that the bond should be there because the synthetic precursor to Formula I is Formula V, which contains the bond. Further, the species in Claim 2 are bicyclic: 3-azabicyclo[3.1.0]-hexyl derivatives and appear on the search report as bicyclic compounds.

Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over **Claims 1-29** of US Serial No. **10/552,502**. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to overlapping subject matter, (specifically when **Q** = $(CH_2)_n$, **n** = 0, and **Z** = NR_{10}). The compounds of the current application are not patentably distinct from those of the **'502** application because of the significant overlap within formula I of each case. Therefore, potential infringements upon the instant application would also be infringements upon the **'502** application.

Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over **Claims 1-10, 15, 17-19, 21, 22, 24, 25, 27-29, 31, 32, 34, 35, 51 & 53** of US Serial No. **10/525,439**. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to overlapping subject matter, (specifically when **X** = no atom

and **Y** = bond). The compounds of the current application are not patentably distinct from those of the **'439** application because of the significant overlap within formula I of each case. Therefore, potential infringements upon the instant application would also be infringements upon the **'439** application.

Claim Objections

Claim 6 is objected to because of the following informalities: the list should include commas between members and the word "and" between the last two species. Appropriate correction is required.

Allowable Subject Matter

The present invention pertains to the 3-azabicyclo[3.1.0]hex-6yl derivatives according to formulae I-IV and methods of using these compounds for the treatment of muscarinic receptor related disorders. The compounds according to formulae I-IV are free of the prior art; nothing known in the art anticipates or renders the compounds of the instant application obvious. Besides the work of the Applicants, no other prior art appears on the structure report.

One skilled in the art would be enabled to make and use the compounds taught herein for the treatment of muscarinic receptor related disorders (such as those listed in **Claims 13-17 & 19**) using the teachings of the Specification in conjunction with the teachings in the prior art.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

Rebecca Anderson, Primary Examiner
for Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: June 21, 2007